Original Article

Clinical outcome in primary versus secondary dengue infection in tertiary care hospital

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Abstract

Introduction: The first reported epidemics of dengue or dengue-like disease occurred in 1779 and 1780 in Egypt and Indonesia and in 1780 in the USA (Philadelphia).[1] It is clear that dengue and other arboviruses with similar ecology had a widespread distribution in the tropics as long as 200 years ago. **Aims and Objectives: To** Study of Serum Aminotransferases Level in Dengue Fever **Methodology:** The study was performed on patients admitted for dengue fever in Aarupadai Veedu Medical College, Puducherry. Total duration of the study was 2 years. Dengue Serology**:** Done by immunochromatographic method.AST and ALT was estimated by IFCC (International Federation of Clinical Chemistry) without pyridoxal phosphate activation. **Result:** It was observed that patients with dengue shock syndrome were in much higher risk for bleeding tendencies as compared to those in the other two groups. It was also observed that patients with secondary dengue infections had a much higher incidence of bleeding as compared to the primary dengue infection of dengue. It was also that the patients who were both secondary infection, they had a higher frequency of hypotension as compared to other group which was only primary infection. It was noted that SGOT and SGPT levels were significantly higher in patients with secondary dengue infection as compared to only primary infection, significant p value (<0.00001). **Conclusion:** The Secondary Dengue infection was associated with clinical outcomes like higher risk for bleeding tendencies, higher frequency of hypotension, SGOT; SGPT levels were significantly higher in patients with secondary dengue as compared to primary dengue infection.

Keywords: Primary dengue infection, Secondary dengue infection Serum Aminotransferase, Dengue Fever, AST, ALT.

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Received Date: 20/11/2015 Revised Date: 26/12/2015 Accepted Date: 16/01/2016

Access this article online	
Quick Response Code:	Website: www.statperson.com
	DOI: 20 January 2016

INTRODUCTION

The first reported epidemics of dengue or dengue-like disease occurred in 1779 and 1780 in Egypt and Indonesia and in 1780 in the USA (Philadelphia).[1]It is clear that dengue and other arboviruses with similar ecology had a widespread distribution in the tropics as long as 200 years ago. Historically, Asia has been the area of highest endemicity, with all four dengue serotypes circulating in the large urban centres in most countries[2,3]. Epidemiological changes in the American region have been the most dramatic; all four viruses are now endemic.[2,3] In the 1980s increased dengue activity was observed in Africa, and all four dengue serotypes have now been documented in Africa[3,4]. Dengue infection, an arthropod-borne viral hemorrhagic fever, continues to be a major challenge to public health, especially in South-East Asia.[5] It has a wide geographical distribution and can present with a diverse clinical spectrum.[6] Although dengue virus is a nonhepatotropic virus, liver injury due to dengue infection is not uncommon and has been described since the 1960s.[7] Hepatic involvement can be characterized by manifestations of acute hepatitis, with pain in the right hypochondrium, hepatomegaly, jaundice, and raised aminotransferase levels. In hepatitis, the levels of these enzymes reach a maximum on the ninth day after the onset of symptoms, and they gradually return to normal levels within three weeks. Although the liver is not the main target organ for this disease, histopathological findings, including centrilobular necrosis, fatty alterations, hyperplasia of the Kupffer cells, acidophil bodies and monocyte infiltration of the portal tract have been detected in patients with dengue hemorrhagic fever (DHF) and dengue shock syndrome

How to site this article: Niloy Gan Chaudhuri, S Vithiavathi, K Sankar. Clinical outcome in primary versus secondary dengue infection in tertiary care hospital. *MedPulse – International Medical Journal* January 2016; 3(1): 84-87. http://www.medpulse.in (accessed 24 January 2016).

(DSS). In most cases, hepatic involvement prolongs the clinical course of this self-limiting viral infection, but it does not constitute a sign of worse prognosis.[2,8] The liver dysfunction could be a direct viral effect or an adverse consequence of dysregulated host immune response against the virus.[2] Severaloutbreaks of dengue infection have been reported from India. However, large clinical studies documenting hepatic involvement in dengue infection, especially in adults, are scarce. Recent development in molecular virology have led to increasing availability of viral gene sequence studies. It has been shown that there is abundant genetic variation within each serotype in the form of phylogenetically distinct clusters of sequences dubbed subtypes or genotypes.[38] A primary dengue infection, defined as the absence of specific anti-dengue IgG antibodies in the first serum sample during the acute phase, with anti- dengue IgM, virus isolation or virus RNA being present, and dengue virus IgG being detected in a later sample[5,6]. Secondary infection can be detected by testing the patients NS1, IgG and IgG all were high during the first day of infection, hence possibly interpreted as primary infection but NS1 and IgM will go down from the second day onwards, and IgG will remain high. Because of this, the interpretation of secondary infection may be made.[5,6]. Secondary infections of dengue, carries a greater risk of dengue hemorrhagic fever and dengue hemorrhagic shock as compared to the primary infection of dengue as shown by few studies[7]. Other theories involving a virulent strain of dengue virus[9] and genetic differences in the hosts[10,11] have been proposed. The association of the introduction of a specific (South-east Asian) genotype of DENV-2 and the appearance of DHF in America suggested that a certain genotype has potential to cause severe dengue (DHF).[12] The finding that the same DENV-2 genotype may cause dengue fever or DHF in Thailand suggested that both virus genotype and secondary infection are important contributing factors in the pathogenesis of DHF.[13]In dengue infections, elevations in serum AST appear to be greater than ALT levels. This differs from the pattern in viral hepatitis, in which ALT levels are usually higher than or equal to AST levels, but it is similar to that seen with alcoholic hepatitis. The exact significance of this pattern seen in dengue is uncertain. It has been suggested that it may be due to excess release of AST from damaged myocytes during dengue infections (Chung *et al*.[14,] but this has not been formally tested. Simultaneous measurement of muscle isoforms of lactate dehydrogenase and creatinine kinase may help further clarify this observation. The elevated AST levels tend to return to normal more rapidly than ALT levels. This is possibly because AST (12.5—22 h) has a shorter half-life than ALT (32—43 h) Hawker. F[15.] Other than haematological abnormalities the main abnormality in dengue fever is hepatic dysfunction in the form of raised SGOT and SGPT levels. Multiple studies had proved that SGOT and SGPT levels were significantly increased in all the forms of dengue and that SGOT level was more increased than SGPT levels.[16, 17, 18,19,20]

MATERIAL AND METHODS

The study was performed on patients admitted for dengue fever in Aarupadai Veedu Medical College, Puducherry. Total duration of the study was 2 years. All the adult patients with clinical features such as fever and later confirmed positive by dengue serology test admitted as inpatients will be included in the study were included into study while, Age >18 years, Chronic liver disease**,** Viral hepatitis (Hepatitis. B, Hepatitis. C)**,** Malaria **(**MP, MF**),** Leptospirosis**,** History of Hepatotoxic drugs, History of alcohol abuse**.** All patients were evaluated with detailed history including age, sex, presenting symptoms; history of co morbid illness; alcohol consumption and use of hepatotoxic drugs were noted. The World Health Organization (WHO) grading system was used to classify patient as having classic dengue fever (DF) and dengue hemorrhagic fever (DHF) (WHO, 1997). Dengue Serology**:** Done by immunochromatographic method.AST and ALT was estimated by IFCC (International Federation of Clinical Chemistry) without pyridoxal phosphate activation.

RESULT

Table 1: Bleeding manifestation in the primary and secondary dengue sub groups

Variables	Total	Bleeding Manifestation	Percentage	P value
IgM positive	60	26	43.33%	0.375
IgMandIgG positive	20	15	75%	0.00278

It was observed that patients with dengue shock syndrome were in much higher risk for bleeding tendencies as compared to those in the other two groups. It was also observed that patients with secondary dengue infections had a much higher incidence of bleeding as compared to the primary dengue infection of dengue.

Table 2: Comparison of bleeding manifestations between primary and secondary dengue infections

Variables	Yes(no of patients)	No(no of patients)	P Value
IgM Positive(N=60)	3	57	<0.00005
IgG and IgM Positive(N=20)	5	15	0.018

It was also that the patients who were both secondary infection, they had a higher frequency of hypotension as compared to other group which was only primary infection.

Table 3: Comparison of LFT in primary and secondary Dengue infection

Liver Function Test	Total Bilirubin	AST	ALT	Total PROTEIN	Serum ALBUMIN	p value
IgM POSITIVE	0.421±0.2448	88.977±59.86	53.881±42.058	2.365±0.288	1.274±0.151	0.000432
IgGandIg G POSITIVE	0.475±0.36	123.195±151.135	77.997±95.018	2.37±0.284	1.249±0.165	<0.00001

It was noted that SGOT and SGPT levels were significantly higher in patients with secondary dengue infection as compared to only primary infection, significant p value (<0.00001).

DISCUSSION

Dengue virus antigen is found predominantly in cells of the spleen, thymus, lymph nodes, Kupffer cells and in the sinusoidal lining cells of liver and alveolar lining cells of the lung. All four dengue serotypes are capable of causing dengue fever or DHF, depending on the immune status and probably age of the host, as DHF occurs almost exclusively in children under the age of 16 years and is associated with secondary dengue infection. A strong association between DHF and secondary dengue infection has led to Halstead's proposed concept of two sequential infections. Based on his in vitro and monkey studies, an antibody-dependent immune enhancement theory had been hypothesized by Halstead[21]: It was suggested that during the second infection with a heterotypic dengue virus which differs from the first one, pre-existing antibody from the first infection fails to neutralize and may instead enhance viral uptake and replication in the mononuclear phagocytes. Such infected cells may then become the target of an immune elimination mechanism which can trigger the production of mediators with activation of complement and the clotting cascade and eventually produce DHF.[21] In Thailand, studies over the last 40 years have demonstrated transmission of all four dengue serotypes,[22] with dengue type 2 as the predominating serotype up to 1990.[23] The studies and experience in Thailand, as well as in Cuba, confirmed the suggestion that the interval between the two dengue infections and the sequences of infecting dengue serotypes, i.e. secondary infection with DENV-2 following DENV-1 infection may be important factors in determining the occurrence and severity of DHF[21,24] The interval between the two infections was first suggested to be 1–5 years following the Cuban experience where the first outbreak of DHF occurred with DENV-2 in 1981 following the outbreak of dengue fever with DENV-1 in 1977. The second outbreak of DHF in Santiago, Cuba in 1997 with DENV-2 after a period of apparent elimination of vectors and dengue virus for 16 years led to two important observations: (1) immune enhancement could occur after a long duration of 20 years and (2) primary DENV2 infection in children less than 16 years did not cause DHF.[25]A study by Vaughn *et al*. revealed that increased dengue disease severity (dengue v/s DHF) correlated with high viraemiatitre, secondary dengue infection and DENV-2 serotype.[26] The most recent study on the role of T cells in the pathogenesis of DHF has described a phenomenon of original antigenic sin.[27] The group has found a paradoxical T cell response in that many of the T cells had a relatively low affinity for the current infecting DENV serotype but showed higher affinity for serotypes which had been encountered before. This phenomenon resulted in delayed elimination of the secondary infecting serotype, allowing further proliferation and high viral load.[27]Other theories involving a virulent strain of dengue virus[55] and genetic differences in the hosts[29,30] have been proposed. The association of the introduction of a specific (South-east Asian) genotype of DENV-2 and the appearance of DHF in America suggested that a certain genotype has potential to cause severe dengue (DHF).The finding that the same DENV-2 genotype may cause dengue fever or DHF in Thailand suggested that both virus genotype and secondary infection are important contributing factors in the pathogenesis of DHF. In our Study we have observed that It was observed that patients with dengue shock syndrome were in much higher risk for bleeding tendencies as compared to those in the other two groups. It was also observed that patients with secondary dengue infections had a much higher incidence of bleeding as compared to the primary dengue infection of dengue. It was also that the patients who were both secondary infection, they had a higher frequency of hypotension as compared to other group which was only primary infection. It was noted that SGOT and SGPT levels were significantly higher in patients with secondary dengue infection as compared to only primary infection, significant p value (<0.00001).

CONCLUSION

The Secondary Dengue infection was associated with clinical outcomes like higher risk for bleeding tendencies, higher frequency of hypotension, SGOT, SGPT levels were significantly higher in patients with secondary dengue as compared to primary dengue infection.

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Source of Support: None Declared
Conflict of Interest: None Declared